CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

MICROBIOLOGY REVIEW

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21-567 **SN:** 000 **DATE REVIEWED:** 3/3/03
Microbiology Reviewer: Lisa K.Naeger, Ph.D.

Sponsor's Name and Address:

Bristol-Myers Squibb
5 Research Parkway
P.O. Box 5100
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Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Initial Submission Dates: December 20, 2002
Pre-Submission Date: November 14, 2002
Correspondence Date: December 20, 2002
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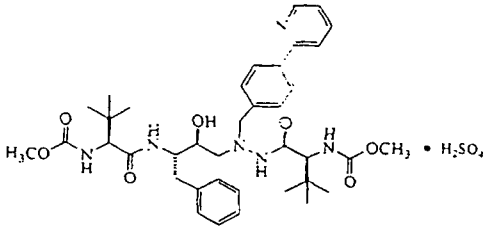
Amendments: N21567 000 (BI)
Correspondence Date: April 1, 2003
CDER Receipt Date: April 2, 2003
Reviewer Receipt Date: April 14, 2003
Review Complete Date: June 18, 2003

Related/Supporting Documents: IND — (BMS), IND —, IND —
— IND — IND —
— DMF No. — DMF No. —
IND — SN-425, NDA — B1 and B2

Product Name(s): Atazanavir (BMS-232632, ATV)
Proprietary: Reyataz™
Non-Proprietary/USAN: Atazanavir sulfate
Code Name/Number: BMS-232632

Chemical Name: Dimethyl (3S, 8S, 9S, 12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazaetradecanedioate sulfate (1:1)

Structural Formula:



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Atazanavir (BMS-232632, ATV)
Molecular Formula: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$
Molecular Weight: 704.9

Dosage Form(s): 100/150/200 mg capsule
Route(s) of Administration: Oral
Pharmacological Category:
Indication(s): Treatment of HIV infection in combination with other antiretroviral agents

Dispensed: Rx X **OTC**_____

Abbreviations: α-1AGP, alpha-1 acidic glycoprotein; APV, amprenavir; ARV, antiretroviral; ATV, atazanvir; CC, cytotoxic concentration; CI, combination index; d4T, stavudine; DC, discontinuation; ddI, didanosine; DNA, deoxyribonucleic acid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IC, inhibitory concentration; IDV, indinavir; LOQ, Limit of Quantification; LPV, lopinavir; moi, multiplicity of infection; mAb, monoclonal antibody; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; pol, polymerase; PPT, polypropylene tubes; PR, protease; RNA, ribonucleic acid; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; RTV, ritonavir; TLOVR, Time to Loss of Virologic Response; TP, triphosphate; SQV, saquinavir; WT, wild-type

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Executive Summary

This original NDA-21567 describes a novel protease inhibitor, atazanavir (ATV), for the treatment of HIV infection in combination with other antiretroviral agents formulated in 100, 150 and 200 mg capsules. Atazanavir is an azapeptide HIV-1 protease inhibitor that exhibits anti-HIV-1 activity with an EC_{50} of 2 to 5 nM against a variety of HIV-1 isolates in several cell-types.

There are currently seventeen FDA-approved anti-HIV drugs including six protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), seven NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), three NNRTIs (delavirdine, efavirenz and nevirapine), and one fusion inhibitor (enfuvirtide). To support ATV use in combination with other antiretroviral agents, the antiviral and cytotoxic effects of ATV in two-drug combinations were examined *in vitro* with all the approved anti-HIV drugs. Results from these studies indicated that the combination of ATV with abacavir and the NNRTIs: delavirdine, efavirenz, and nevirapine are additive-antagonistic. Combinations of ATV with the protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and the NRTIs (didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) showed additive antiviral activity interactions. Minimal to no cellular cytotoxicity was observed with any of these compounds alone or in combination with ATV.

To assess the potential for ATV resistance development and to identify amino acid changes associated with ATV resistance, the applicant utilized *in vitro* selection. Three HIV strains were passaged at increasing concentrations of ATV and resistant viruses were selected after 4-5 months at final ATV concentrations of 200-500 nM. These selected viruses exhibited 93- to 183-fold increases in ATV resistance, which is the change in the IC_{50} value compared to the wild-type parental strain. The key amino acid changes in the protease were I50L, which is different from the amprenavir-associated resistant mutation I50V, and I84V, A71V, and M46I, which are associated with resistance to other protease inhibitors.

The applicant has provided evidence that ATV resistance corresponds to the I50L and A71V mutations by constructing recombinant viruses from eight clinical isolates. These viruses with the I50L with or without the A71V mutation show 2- to 17-fold changes in their IC_{50} values for ATV compared to the wild-type parental strain. Furthermore, the addition of the I50L mutation results in replication-impaired viruses with a five-fold defect. The A71V mutation restores some viability to the virus suggesting it may be a compensatory mutation. Importantly, recombinant viruses containing the I50L mutation either with our without A71V remain susceptible to other protease inhibitors suggesting treatment-naïve patients who develop the I50L mutation in their virus would still have other treatment options.

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Atazanavir-resistant isolates have been obtained from patients on atazanavir therapy. Fourteen ATV–resistant clinical isolates from trials of treatment-naïve subjects who were virologic failures developed the I50L mutation. Development of the I50L mutation ranged from 12-80 weeks of ATV therapy, averaging 50 weeks. An examination of the clinical isolates developing the I50L mutation showed an average 11-fold change from baseline for ATV and an increased susceptibility to approved protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) indicating that other protease inhibitors have activity against virus with the I50L mutation.

Mutations that developed in 36 isolates that were ATV-resistant and virologic failures from the trials of treatment-experienced subjects included A71V, I84V, L90M, N88S/D, M46I and I50L - all of which were observed in the *in vitro* selection experiments. These ATV-resistant isolates showed a median 12-fold change in ATV susceptibility and were highly cross-resistant with other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). Four of the 36 isolates developed the I50L mutation on ATV treatment.

The response based on baseline genotype showed that if a virus had an I84V, L90M, A71V, N88S/D, or M46I mutation at baseline, the response to ATV treatment was not as effective as comparative treatments. Furthermore, ATV loses its effectiveness as clinical isolates become resistant to three or more protease inhibitors with > 80% of isolates resistant to 4 or 5 other protease inhibitors also resistant to ATV.

In summary, there are different possible resistance pathways for ATV. ATV has a unique pathway in treatment-naïve patients with the development of a key mutation, I50L. The I50L mutation is specific for ATV resistance and is the predominant mutation developing in antiretroviral therapy-naïve patients. Importantly, viruses with the I50L mutation remain susceptible to the other approved protease inhibitors. The other pathway occurring in treatment-experienced patients follows a common PI-resistance pathway with the development of mutations associated with resistance to multiple protease inhibitors. Mutations L90M, I84V, N88, and A71V/T appear to confer ATV resistance and reduce clinical response to ATV. The evidence suggests that if other protease inhibitor mutations are present, ATV resistance develops primarily through the later pathway rather than the I50L pathway. Finally, if isolates are resistant to three or more protease inhibitors, they are more likely to be ATV resistant.

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1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA for atazanavir 100, 150 and 200 mg capsules is approvable with respect to microbiology for the treatment of HIV in combination with other anti-HIV agents. It offers a simple once-a-day regimen with the benefit of reduced lipid and triglycerides compared to lopinavir. ATV has a unique resistance profile in antiretroviral-naïve patients with the development of the I50L mutation, which retains susceptibility to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). In antiretroviral-treatment-experienced patients, the use of ATV should depend on ATV susceptibility determined by genotypic and/or phenotypic assays. ATV is highly cross-resistant with other protease inhibitors against HIV-1 isolates from treatment-experienced patients.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

1. Submit analysis of protease cleavage sites in ATV- resistant patients from studies 034, 043 and 045 by 1Q04.

2. Follow a cohort of patients who failed on ATV treatment and developed the I50L mutation on new physician-selected PI regimens for 48 weeks compared to an NNRTI-failure/PI-naïve patient cohort and determine treatment response, baseline genotypes and phenotypes, and genotypes and phenotypes of virologic failures. Protocol should be submitted by 1Q04.

3. Test the antiviral activity *in vitro* of atazanavir against multiple isolates of HIV-2 and non-clade B subtypes of HIV-1.

2. Summary of OND Microbiology Assessments

2.1. Brief Overview of the Microbiological Program

2.1.1. Non-clinical

Atazanavir (ATV, BMS-232632) is an azapeptide HIV-1 protease inhibitor that exhibits anti-HIV activity with an EC_{50} value of 2 to 5 nM against a variety of HIV isolates grown in cell cultures of PBMCs, macrophages, CEM-SS, and MT-2 cells. ATV specifically and selectively blocks the cleavage of the viral Gag and Gag-Pol precursor proteins in HIV-infected cells preventing viral particle maturation. Cytotoxicity with ATV is observed at concentrations >5,000-fold higher than that required for anti-HIV activity. Drug combination studies using

ATV with abacavir and NNRTIs demonstrated additive-antagonism and with NRTIs and PIs demonstrated additive effects.

HIV-1 resistant to ATV was selected from *in vitro* selection experiments in three different HIV-1 strains. These ATV-resistant HIV-1 isolates showed a 93- to 183-fold decrease in susceptibility to atazanavir compared to parental wild-type virus. Genotypic analyses indicated that I50L, A71V, N88S/D and I84V substitutions appeared to be key changes with possible roles in ATV resistance. Direct evidence for a role of the I50L mutation in ATV resistance was obtained by constructing recombinant viruses with the protease gene from clinical isolates. ATV resistance corresponded to the presence of the I50L and A71V mutations in the protease coding sequence. Results showed that the I50L mutation, sometimes combined with A71V and other changes, appears to be a signature substitution for ATV and mediates increased susceptibility to other PIs by an unknown mechanism. Clinical isolates resistant to one or two currently approved PIs (the majority nelfinavir-resistant with D30N mutations) were generally susceptible to ATV. Assessment of clinical isolates resistant to one or more PIs in patients never exposed to ATV showed that susceptibility to ATV decreased as the level of cross-resistance to other PIs increased.

2.1.2. Clinical Microbiology

Genotypic and phenotypic evaluation of clinical isolates from ATV-treated patients designated as virologic failures with decreased ATV susceptibility demonstrated that ATV displayed different resistance patterns depending on the patient population. When ATV was used in patients with no previous antiretroviral experience, clinical isolates developed a unique I50L mutation frequently accompanied by an A71V change. The I50L mutation resulted in ATV resistance, impaired viral growth, and increased susceptibility to other PIs. In contrast, isolates from treatment-experienced patients treated with ATV and ATV/SQV generally did not develop the I50L mutation but acquired several additional amino acid changes including I84V, L90M, M46I and N88S/D. These additional mutations in protease also conferred cross-resistance to the other approved PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). A significantly higher percentage of the clinical isolates from ATV treatment arms with PI mutations I84V, L90M, A71V, M46I and N88S/D at baseline were virologic failures compared to isolates from other treatment arms. This suggests that these mutations in the HIV-1 protease are detrimental to ATV antiviral activity and may affect the virologic response to ATV treatment clinically.

3. Administrative

3.1. Reviewer's Signature(s)

_____
[Lisa K. Naeger, Ph.D.]
Microbiologist, HFD-530

3.2. Concurrence

HFD-530/Signatory Authority _____ Signature _____ Date
HFD-530/Micro TL _____ Signature _____ Date

3.3. CC Block

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/s/

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